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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/932,129	08/16/2001	Bob D. Brown	OASBIO.002C1	4332

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/16/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/932,129	BROWN, BOB D.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *0/28/02, 12/2/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 22-49* is/are pending in the application.

4a) Of the above claim(s) *1-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed October 22, 2002. Currently, claims 1-17, 22-49 are pending. Claims 1-17 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group II, claims 22-49 in Paper No. 10 is acknowledged.

Priority

3. This application claims priority to PCT US00/09230, filed April 7, 2000 and provisional application 60/128,378, filed April 8, 1999.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 22, 27-29, 31-34, 36, 37, 42-46, 48-49 are rejected under 35 U.S.C. 102(e) as being anticipated by Ulanovsky et al. (US Pat. 6,197,556 B1, filed May 7, 1997).

Ulanovsky et al. (herein referred to as Ulanovsky) teaches a method of nucleic acid amplification using modular branched primers. The stem portions of branched primers are constant and bind portions of variable modules together to give specificity to the initial priming (extension) yet allow amplification using conventional primers to proceed (col. 2, lines 23-26). As seen in Figure 2(1)- Figure 2(4), a pair of branched primers are extended in both the forward and reverse directions followed by a pair of unbranched primers (limitations of Claim 22, 33-34). A branched pair of primers is comprised of a front module, a front arm, a back module and a back arm (figure 4). The method includes annealing the template to a first branched primer which included both front and back oligonucleotide modules. Ulanovsky teaches that "front" refers to the 3' extending (downstream) sequence and "back" refers to the 5' end (upstream). The stem segments are complements of each other and anneal to form the stem of the branched primer (col. 2, lines 30-41). The arm segments is complementary to a nucleotide sequence site in a template to be amplified (col. 2, lines 43-50). The first initial extension strand is annealed to a reverse primer which may be either branched or not to form a second initial extension strand (col. 2, lines 50-55). Then the products are amplified by using amplification primers that include a reverse primer and/or at least one primer homologous to the stem sequence of the first and/or second branched primer (col. 2, lines 55-60). The strand resulting from the extension of the first initial

primer is us used as a template and the two PCR primers are a reverse primer and the front module of the first initial primer (or a universal primer homologous to the stem of the first module)(col. 9, lines 45-55). Ulanovsky also teaches that the arm of each oligonucleotide module sequence preferably contains at least one artificial base to reduce steric hindrance that may be caused by proximity of the stem to the extension point and/or to enhance the annealing stability. Theres base modifications can be either of bases or backbones in modular primer that improve the stability of annealing, such as PNA, methyl phosphonate, 5-methylcytidine and 2-aminoadenosine (col. 2, lines 60-67; col 13, lines 17-20)(limitations of Claim 27-28, 42-45). As seen in the example, the PCR amplification is demonstrated using four branched DNA primers (col. 18)(limitations of Claim 29, 31, 46, 48). Ulanovsky teaches using a thermostable polymers for the initial extension such as ampliTaq and Stoffel fragment (col. 2, lines 55-65)(limitations of Claim 32, 49). Figure 4 illustrates the first target binding region comprising at least 6 nucleotides, namely 6 nucleotides (limitations of Claim 36-37).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 30, 35, 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulanovsky et al. (US Pat. 6,197,556 B1, filed May 7, 1997).

Ulanovsky et al. (herein referred to as Ulanovsky) teaches a method of nucleic acid amplification using modular branched primers. The stem portions of branched primers are constant and bind portions of variable modules together to give specificity to the initial priming (extension) yet allow amplification using conventional primers to proceed (col. 2, lines 23-26). As seen in Figure 2(1)- Figure 2(4), a pair of branched primers are extended in both the forward and reverse directions followed by a pair of unbranched primers (limitations of Claim 22, 33-34). A branched pair of primers is comprised of a front module, a front arm, a back module and a back arm (figure 4). The method includes annealing the template to a first branched primer which included both front and back oligonucleotide modules. Ulanovsky teaches that "front" refers to the 3' extending (downstream) sequence and "back" refers to the 5' end (upstream). The stem segments are complements of each other and anneal to form the stem of the branched primer (col. 2, lines 30-41). The arm segments is complementary to a nucleotide sequence site in a template to be amplified (col. 2, lines 43-50). The first initial extension strand is annealed to a reverse primer which may be either branched or not to form a second initial extension strand (col. 2, lines 50-55). Then the products are amplified by using amplification primers that include a reverse primer and/or at least one primer homologous to the stem sequence of the first and/or second branched primer (col. 2, lines 55-60). The strand resulting from the extension of the first initial primer is us used as a template and the two PCR primers are a reverse primer and the front

module of the first initial primer (or a universal primer homologous to the stem of the first module)(col. 9, lines 45-55). Ulanovsky also teaches that the arm of each oligonucleotide module sequence preferably contains at least one artificial base to reduce steric hindrance that may be caused by proximity of the stem to the extension point and/or to enhance the annealing stability. Theres base modifications can be either of bases or backbones in modular primer that improve the stability of annealing, such as PNA, methyl phosphonate, 5-methylcytidine and 2-aminoadenosine (col. 2, lines 60-67; col 13, lines 17-20)(limitations of Claim 27-28, 42-45). As seen in the example, the PCR amplification is demonstrated using four branched DNA primers (col. 18)(limitations of Claim 29, 31, 46, 48). Ulanovsky teaches using a thermostable polymers for the initial extension such as ampliTaq and Stoffel fragment (col. 2, lines 55-65)(limitations of Claim 32, 49). Figure 4 illustrates the first target binding region comprising at least 6 nucleotides, namely 6 nucleotides (limitations of Claim 36-37).

Ulanovsky does not specifically teach a library of first oligonucleotides primers which is greater than 65,536 oligonucleotides. Moreover, Ulanovsky does not specifically teach using an RNA target sequence.

Ulanovsky teaches that priming libraries may be used which have variable positions for all possible sequences. Ulanovsky teaches that the library may be 5, 6, or 7 variable positions. Ulanovsky does not specifically limit the number of positions. An 8-mer variable oligonucleotide would have 65,536 oligonucleotides within the library. A library with 9 variable positions would create 262,144 oligonucleotides. Thus, any oligonucleotide of 9 or more nucleotides which had variables at each position would

satisfy the limitation. The ordinary artisan would be motivated to increase the possible binding sites in a random template sequence to increase specificity and sensitivity.

With respect to RNA, Ulanovsky clearly teaches that the "invention should not be limited to DNA and should include the possibility of one or both strands of the above description being RNA strands, as well as the nucleic acid polymerases being not only DNA but also RNA polymersase (col. 22, lines 5-15). Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the method of Ulanovsky to encompass the detection of RNA nucleic acids. Detecting RNA nucleic acids would expand the genus of detectable nucleic acids. The suggestion in Ulanovsky clearly indicates that one would have motivation to detect RNA.

6. Claims 23-26, 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulanovsky et al. (US Pat. 6,197,556 B1, filed May 7, 1997) as applied to Claims 30, 35, 47 above and further in view of Stefano et al. (US Pat. 6,287,772, filed April 29, 1998).

Ulanovsky does not specifically teach using a linker between the first stem region and the target binding region.

However, Stefano teaches in Figure 2A a linker between the first stem region and the target binding region. Stefano teaches PNA is a polyamide (limitations of Claims 23-26, 38-41)(col. 7, lines 14-15). Moreover Stefano teaches spacers are used to minimize the adverse effects that bulky labeling reagents might have in hybridization

properties of non-nucleic acid probes (col. 7, lines 30-40). Linkers typically induce flexibility and randomness into the probe or otherwise link two or more nucleobase sequences of a probe or component polymer (col. 7, lines 30-40). Stefano teaches that many linker/spacer moieties are known in the art and provides a variety (col. 7).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have added a spacer/linker, as taught by Stefano, into the primer modules of Ulanovsky for the expected benefit taught by Stefano. Stefano teaches that spacers/linkers are used to minimize adverse effects, increase flexibility and randomness. Thus, the ordinary artisan would have been motivated to incorporated a spacer/linker into the branched probe of Ulanovsky between the arm and the target region to minimize adverse effects, and increase flexibility.

Conclusion

7. No claims allowable over the art.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Egholm et al. (US Pat. 6,451,588, September 2002) teaches multipartite high-affinity nucleic acid probes which comprise a flexible linker (see Figure 1A).

B) Weston et al. (US Pat. 6,391,593, May 21, 2002) teaches methods of detecting nucleic acid sequences using modified nucleic acid probes (see Figure 1).

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
January 9, 2003

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600